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ICI 180080, a novel selective thromboxane receptor antagonist: synthesis and relative activity

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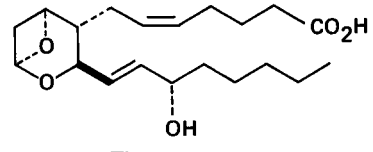
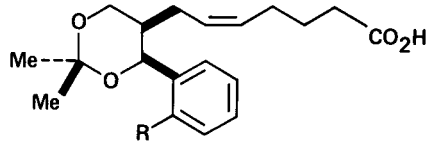
The preparation of a novel potent thromboxane receptor antagonist ICI 180080, 5(Z)-7-[2,2-dimethyl-4-(2-hydroxyphenyl)-1,3-dioxan-*cis*-5-yl] heptenoic acid, is described together with its methyl ether and methyl ester. Thromboxane antagonist pA_2 data against U 46619 is presented for rabbit thoracic aorta in-vitro (ICI 180080, pA_2 = 7·5). The relative antagonist pA_2 values obtained are discussed in terms of the chemical structure of the molecules. The potent activity of ICI 180080 is attributed to a specific orientation of the phenolic oxygen, due to an intramolecular hydrogen bond.

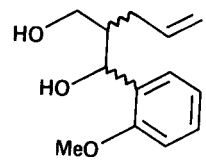
Study of the pharmacological activity of 5(Z)-7-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoic acid ICI 159995 (**Ia**) (Jessup et al 1985) has shown that it represents a novel type of thromboxane receptor antagonist. The characteristic chemical features of the molecule which differentiate it from thromboxane A_2 are (Brewster et al 1986): a 1,3-dioxane ring, a phenyl ring in place of the conventional prostaglandin bottom side chain and *cis* stereochemistry of the ring substituents. We report that introduction of an *ortho*-hydroxy substituent in the phenyl ring of **Ia** to give 5(Z)-7-[2,2-dimethyl-4-(2-hydroxyphenyl)-1,3-dioxan-cis-5-yl]-heptenoic acid ICI 180080 (**Ib**) leads to an order of magnitude increase in the thromboxane antagonist potency (pA_2 = 6·3 (**Ia**), 7·5 (**Ib**) Table 1). The full pharmacology of ICI 180080 is described by Jessup et al (1986) and herein the synthesis of 180080 is elaborated, together with some related compounds. The compounds described are compared on the basis of their chemical structure and antagonism at the rabbit thoracic aorta in-vitro following a challenge with U 46619, the standard thromboxane mimetic. In this way the structural feature responsible for the 'step-jump' in thromboxane antagonist activity is considered. The method and materials used to obtain the thomboxane antagonist pA2 values (Table 1) are described fully by Jessup et al (1986).



Thromboxane A_2



Structure **I**: **a**, R = H; **b**, R = OH; **c**, R = OMe; **d**, R = OH, methyl ester



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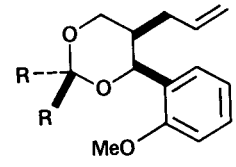


Structure **III**: **a**, R = Me; **b**, R = H

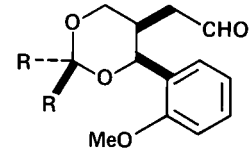
Table 1. Relationship between thromboxane antagonism and chemical structure.

Compound	pA_2 vs U 46619* on rabbit thoracic aorta
Ia R = H (ICI 159995)	6·3
Ib R = PH (ICI 180080)	7·5
Ic R = OMe	6·0
Id R = OH, methyl ester	7·0
V	6·0

* (15*S*)-hydroxy-11x,9x-(epoxymethane)prosta-5Z,13E-dienoic acid

Chemistry

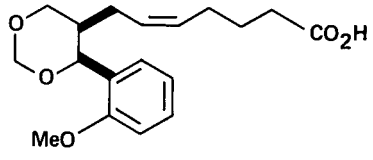
The dioxane **Ib** and its methyl ether **Ic** were prepared via ring closure of the appropriate diol **II** (Brown & Foubister 1985). Thus **II** and 2,2-dimethoxypropane in the presence of *p*-toluene sulphonic acid gave a mixture of dioxane diastereoisomers with the aryl and allyl groups respectively *cis* and *trans*. Separation of the *cis* diastereoisomers **IIIa** was achieved by flash column chromatography. Ozonolysis in methylene chloride, followed by reduction with triphenyl phosphine afforded the aldehyde **IVa**, which was not characterized but was allowed to react with (4-carboxy-



Structure **IV**: **a**, R = Me; **b**, R = H

* Correspondence.

butyl)triphenylphosphonium bromide in a conventional Wittig reaction in the presence of potassium t-butoxide to give the methyl ether **Ic**. Demethylation of **Ic** with pyridine hydrochloride resulted in cleavage of the acidic side chain, but sodium thioethoxide in dimethylformamide gave the phenol **Ib**. The dioxane **V** was also prepared from diol **II**. Ring closure with methylene bromide in the presence of potassium hydroxide proceeded to give the dioxane **IIIb** after chromatography. Oxidation of **IIIb** with osmium tetroxide and sodium periodate afforded the aldehyde **IVb** as an uncharacterized intermediate which was converted by Wittig reaction to **V** as described for **IVa**.



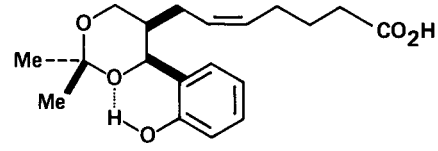
Structure **V**

The carboxylic acid methyl ester (**Id**) of **IV** was prepared by reacting **Ib** with potassium carbonate in methanol, which gave the potassium salt of **Ib**. This salt was allowed to react with methyl iodide in anhydrous 1,3-dimethyl-3,4,5,6-tetrahydro-2[1*H*]-pyrimidinone (DMPU) to give **Id**.

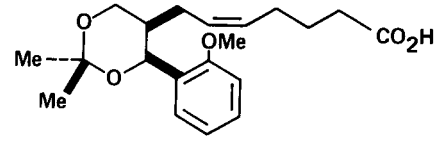
Discussion

The results displayed in Table 1 summarize the pA_2 values obtained against the thromboxane agonist U 46619 on rabbit thoracic aorta and show that all five compounds are thromboxane antagonists. Although the potency of **Ia**, **Ic** and **V** were similar, that of ICI 180080 (**Ib**) and its ester (**Id**) was significantly greater. The common structural feature of **Ib** and **Id** which distinguishes them from the three lesser active compounds is the hydroxyl group in the phenyl ring. This distinctive hydroxyl group could have three effects on the molecule which could influence binding at the receptor: electron donation to the phenyl ring, overall lowering of the lipohilicity of the molecule, and the potential to form an intramolecular hydrogen bond to the 3-oxygen of the 1,3-dioxane ring.

Considering first the electron donating effect of the hydroxyl group, Hammett σ values for aromatic substituents (Hansch et al 1973) show that the influence of a hydroxyl group would be very similar to that of the methoxyl group found in the lesser active **Ic**. Thereby electron donation appears not to be relevant to the relative activities of **Ib** and **Ic**. Secondly it is unlikely that the ability of the hydroxyl group to lower the lipophilicity of the molecule is responsible for the increased potency of ICI 180080. If **Ic** is compared with **V** (Table 1) they exhibit the same thromboxane antagonist acivity but **V** would be less lipophilic because of the absence of two methyl groups on the 1,3-dioxane ring. The nature of the hydrogen bonding of the phenolic hydroxyl group of ICI 180080 was examined by studying the infrared spectrum of its pharmacologically active ester **Id**. It was necessary to use this ester because the absorptions due to the phenolic hydroxyl of **Ib** were obscured by carboxyl absorptions. No free OH absorptions were observed in the infrared spectrum of **Id** at 3590 cm^{-1} in methylene choride, but a strong single band at 3340 cm^{-1} was observed corresponding to an intramolecular hydrogen bond. Thus the most favoured position for the hydroxyl group would be to lie close to the 3-oxygen of the 1,3-dioxane ring as shown in structure **VI**. This situation contrasts sharply with the less active methoxy compounds **Ic** and **V**. In these two compounds the repulsive dipole interaction between the 3-oxygen of the 1,3-dioxane ring and the methoxyl oxygen would cause rotation of the phenyl ring so that the methoxyl group was as far away as possible from the 3-oxygen atom, as in stucture **VII**. Thus it appears that



Structure **VI**



Structure **VII**

the relative position of the hydroxyl and methoxy groups in **Ib** and **Ic** are significantly different. The other possible explanation of the relative antagonist activity of **Ib** and **Ic** is that the phenolic group does not specifically influence the molecule, but binds directly to the thromboxane receptor. This explanation of the 'step-jump' in activity requires that the intramolecular hydrogen bond is broken. Infrared studies show that this bond is not broken in solution until solvent polarity is increased to that of DMSO, indicating that the hydrogen bond is strong. Breaking of the hydrogen bond would not be energetically favoured in the aqueous-lipophilic environment of a drug receptor. Thus the explanation of the 'step-jump' in activity involving a specific orientation of the phenyl ring is preferred.

Preparative work

Melting points are uncorrected. ^1H NMR spectra were recorded on a Varian EM390 (90 MHz), mass spectra on a MS 902 Kratos (AEI) and IR spectra on a Digilab ST5 20E spectrometer. Assigned structures were supported by microanalyses and the characteristic NMR data quoted.

*(4,5-*cis*)5-Allyl-2,2-dimethyl-4-(2-methoxyphenyl)-1,3-dioxane* (**IIIa**)

2-Allyl-3-hydroxy-3-(2-methoxyphenyl) propanol (**II**) (4·7 g) and *p*-toluenesulphonic acid (100 mg) were stirred (18 h) in 2,2-dimethoxy propane (100 ml). The mixture was diluted with ethyl acetate and washed with sodium hydrogen carbonate solution. The ethyl acetate was dried ($MgSO_4$) and evaporated to yield an oil. This was purified by flash column chromatography on silica gel in 4% ethyl acetate-hexane to give the *cis* diastereoisomers (**IIIa**) (3·1 g, 59%) m.p. 79–82 °C; (Found: C, 72·9; H, 8·6. $C_{16}H_{22}O_3$ requires C, 73·3; H, 8·4%). δ ($CDCl_3$) 1·5 (s, 6H), 2·32 (m, 1H) and 5·44 (m, 1H). Further elution gave the *trans* diastereoisomers (1·1 g, 20%) m.p. 61–64 °C; (Found: C, 73·1; H, 8·6 $C_{16}H_{22}O_3$ requires C, 73·3; H, 8·4%), δ ($CDCl_3$) 1·59 (d, 6H), 1·98 (m, H) and 5·18 (d, 1H).

*5(Z)-7-[2,2-Dimethyl-4-(2-methoxyphenyl)-1,3-dioxan-*cis*-5-yl]heptenoic acid* (**Ic**)

A solution of the olefin (**IIIa**) (1·1 g) in dichloromethane (60 ml) at −70 °C was treated with ozone until it became purple. Triphenyl phosphine (1·72 g) was then added and the mixture stirred (18 h). The solvent was evaporated and the residue triturated with hexane with decantation. The residue was purified by flash column chromatography on silica gel in 16% ethyl acetate–hexane to give as an oil the aldehyde (**IVa**) (910 mg, 82%) ν CO 1720 cm^{-1}, δ ($CDCl_3$) 2·6 (m, 1H), 5·4 (d, 1H) and 9·5 (s, 1H). A solution of (4-carboxybutyl)triphenylphosphonium bromide (4·43 g) and potassium t-butoxide (2·24 g) in THF (50 ml) prepared at 0–5 °C, was stirred (45 min) then treated with a solution of **IVa** (900 mg) in THF (15 ml). After 1·5 h, water (50 ml) was added and the THF evaporated. The mixture was washed with ethyl acetate, acidified with acetic acid and extracted with ethyl acetate. Evaporation and purification by flash column chromatography on silica gel in toluene, ethyl acetate, acetic acid (80, 20, 2, v/v) gave after crystallization from heptane, as a colourless solid, **Ic** (680 mg, 57%) m.p. 112–114 °C; (Found C, 69·2 H, 8·1 C_{20} H_{28} O_5 requires C, 68·9 H, 8·1%) δ ($CDCl_3$) 1·98 (m, 6H) and 5·31 (m, 2H). *m/z* 349 (M + 1).

*5(Z)-7-[2,2-Dimethyl-4-(2-hydroxyphenyl)-1,3-dioxan-*cis*-5-yl]heptenoic acid* (**Ib**)

The acid **Ic** (104 mg) was refluxed (70 min) with a 0·5 M solution of sodium thioethoxide in DMF (2·1 ml). The cooled mixture was diluted with water, acidified with acetic acid and extracted with ethyl acetate. Evaporation of the ethyl acetate and purification of the residue by flash column chromatograhy on silica gel in toluene, ethyl acetate, acetic acid (80, 20, 2, v/v) gave after crystallization from ethyl acetate–hexane, **Ib** as a colourless solid (74 mg, 74%) m.p. 76–79 °C; (Found: C, 68·3; H, 8·0 C_{19} H_{26} O_5 requires C 68·2; H, 7·8%) δ ($CDCl_3$) 6·87 (m, 3H) and 7·15 (m, 1H). *m/z* 334 (M^+).

*(4,5-*cis*)5-Allyl-4-(2-methoxyphenyl)-1,3-dioxane* (**IIIb**)

The diol (**II**) (8·9 g), potassium hydroxide (16·0 g) and dibromomethane (10·5 g) were stirred (96 h) in DMSO (100 ml). The mixture was diluted with water and extracted with ethyl acetate. Evaporation of the ethyl acetate and purification by flash column chromatography in 10% ethyl acetate-hexane gave **IIIb** as an oil (1·4 g, 17%); δ ($CDCl_3$) 3·8 (s, 3H), 5·00 (m, 5H), 5·45 (m, 1H) and 7·26 (m, 4H). *m/z* 234 (M^+).

*5(Z)-[4-(2-Methoxyphenyl)-1,3-dioxan-*cis*-5-yl] heptenoic acid* (**V**)

A solution of **IIIb** (1·4 g) in t-butanol (10 ml) was stirred (6 h) with sodium periodate (2·93 g) and osmium tetroxide (100 mg) in water (50 ml) and t-butanol (200 ml). The mixture was diluted with water and extracted with ethyl acetate. The ethyl acetate was evaporated and the residue purified by flash column chromatography on silica gel in 15% ethyl acetate-hexane to give the aldehyde (**IVb**) as a colourless solid (1·2 g, 85%) m.p. 101–103 °C ν_{CO} 1720 cm^{-1}.

The aldehyde (**IVb**) (1·2 g) was treated with Wittig reagent and potassium t-butoxide in a similar manner to that of **IVa** to give **V** as a colourless solid (1·1 g, 68%) m.p. 74–76 °C; (Found: C, 68·0; H, 7·9 C_{18} H_{25} O_5 requires C, 67·5; H, 7·6%) δ ($CDCl_3$) 1·90 (m, 9H), 4·91 (d, 1H) and 5·23 (m, 4H). *m/z* 320 (M^+).

*Methyl-5-(Z)-7-[2,2-dimethyl-4-(2-hydroxyphenyl)-1,3-dioxan-*cis*-5-yl]heptenoate* (**Id**)

Potassium carbonate solution (13·3 ml, 0·05 M) and **Ib** (200 mg) were stirred (2 h) in methanol (10 ml) and the solvents evaporated to dryness: to the residue in 1,3-dimethyl-3,4,5,6-tetrahydro-2[1*H*]-pyrimidinone (DMPU) (10 ml), iodomethane (0·15 ml) was added. After stirring (2 h) at room temperature the mixture was diluted with water. Extraction with ethyl acetate and evaporation gave **Id** as a colourless oil (180 mg, 78%); δ ($CDCl_3$) 3·7 (s, 3H), ν_{CO} 1735 cm^{-1}, *m/z* 349 (M + 1).

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